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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 2/19/04. Claims 21-27 have been cancelled. Claim 28 has been added. Claims 1-20 have been amended. Claims 1-20 and 28 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein and therefore, this action is not final.

Drawings

Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see enclosed form PTO-948.

Priority

Applicants have attempted to insert a specific reference to earlier filed applications in an amendment filed 2/19/04. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months

from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Response to Arguments-Priority

Applicants' state on page 8 of the amendment filed 2/19/04 that the office action summary appears to indicate that copies of the certified copy of the foreign priority document *have not* **and** *have* been received.

The statements that *none* (in section 13A) of the certified copies of been received (13A choice 3) are part of a two step statement. The two selections are not meant to be contradictory but complementary and together state that the certified copies have not been received.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 9-14 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague and indefinite in that the metes and bounds of "the N-terminus of the structural protein" are unclear. The N-terminus is not defined as a domain or a specific set of base pairs but is a vaguely defined region for which there is no clear beginning or end. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and restated here.**

Claim 4 recites the limitation "the protein-cell membrane receptor interaction" in claim 1. There is insufficient antecedent basis for this limitation in the claim. **This is a new rejection.**

Claim 9 is vague and indefinite in that the metes and bounds of "the insertion is a cell membrane receptor ligand, a Rep protein..." are unclear. It is unclear how an insertion **is** a ligand or a protein or a peptide. Furthermore, it is unclear if the insertion is all of the listed ligands and proteins or one of them due to the use alternatively of "or" and "and/or". **This is a new rejection.**

Claim 10 is vague and indefinite in that the metes and bounds of the list of ligands is unclear. The group of ligands is unclear due to the use alternatively of "or" and "and/or". Furthermore, integrin is listed twice in the list. **This is a new rejection.**

Claims 11-13 are vague and indefinite in that the metes and bounds of "cleavage sites" are unclear. The claims recite that insertions occur at various cleavage sites and, therefore, a reference sequence with restriction sites is required to practice the claimed invention. However, there is no reference sequence provided in the specification or the claims so that the location of the cleavage sites can be known. However, applicants are cautioned that addition of a sequence listing to the specification may constitute New Matter. **This is a new rejection.**

Claims 13-14 are vague and indefinite in that the metes and bounds of "one or more insertions" are unclear. It is unclear what is inserted. **This is a new rejection.**

Claim 17 is unclear in reciting that the structural protein is in the form of an AAV particle particularly a capsid. It is unclear how a structural protein **is** in the form of a viral particle as a particle is comprised of a variety of proteins and viral DNA. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and restated here.**

Claim 17 is vague and indefinite in that the metes and bounds of "A structural protein" are unclear. Due to the recitation of "a", it is unclear if this is the same protein in claim 1 or a separate one. **This is a new rejection necessitated by applicants' amendment.**

Response to Arguments-35 USC § 112, second paragraph

Applicants traverse the rejection under 35 U.S.C 112, second paragraph on pages 10-11 of the amendment filed 2/19/04. Applicants traverse the rejection of claim 3 stating that the term "N-terminus" is readily understood by one of skill in the art. The rejection of this claim in a 102 rejection suggests that the Office recognizes the well-accepted meaning of the term. As to the rejection of claim 17, applicants argue that it is clear that the claim covers a mutated structural

protein having all the characteristics set forth in claim 1 and in addition is present in a viral particle.

Applicant's arguments filed 2/19/04 have been fully considered but they are not persuasive. Claim 3 recites a structural protein with mutations in the N-terminus. The term "N-terminus" strictly defines the alpha amide end that is not involved in peptide bond formation. However, the term N-terminus has another well-accepted meaning in the art, to describe the portion of the protein associated with this N-terminus. The length of the N-terminus of a protein is specific in some cases but usually is not. In the instant case, AAV structural proteins do not have a defined N-terminus and in this case, it would not be clear upon reviewing the art what would constitute potential infringement. Furthermore, Mamounas et al teach that a targeting ligand is fused to the N-terminus of the structural protein and as such means the alpha amide end of the molecule. Claim 17 recites that the structural protein is in the form of an AAV particle. As recited the protein itself is said to form an AAV particle. It appears applicant intend that the structural protein is a component of an AAV particle and not is in the form of an AAV particle. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). During prosecution, claims must be interpreted as broadly as their terms reasonably allow. Applicants would like to rely on descriptions of the invention that are not reasonably applied to the claims as written.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of structural proteins with at least one mutation that is capable of particle formation and results in the increased infectivity of viruses containing the mutated structural protein. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and restated here. The rejection has been extended to newly added claim 28.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The instantly claimed invention recites a mutated structural protein that retains that ability to from particles that have increased infectivity. Applicants teach that the mutation by way of point mutations, mutations of several amino acids, deletion or insertion mutations and

combinations of these mutations ultimately alter cell-targeting specificity with increased infectivity. Specifically, the specification teaches insertion of a laminin P1 ligand into VP1 and VP3 (pages 16-20). One viral particle that results form an insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of M07-LP1-R and B16F10 cells. It is also mentioned that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. The disclosure of insertion of the P1 ligand at amino acid 587 to alter specificity to the two cell types is not accompanied by a disclosure as to the relative properties or a correlation between structure of this mutation and its ability to alter infectivity. Therefore, there is no clear description of the structural or functional characteristics required for any other mutations to increase infectivity. Given the large number of mutations envisioned by the invention and the diversity of the cellular receptors and ligands encompassed by the claims and the inability to determine which mutation will increase infectivity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Arguments-35 USC § 112, first paragraph

Applicants traverse the rejection of claims under 35 U.S.C 112, first paragraph on pages 12-14 of the amendment filed 2/19/04. Applicants argue that the basis for the rejection is in error. Applicants state that the production of a mutated structural protein is not an "empirical" process but one based on scientific methodologies determined by structure and protein

alignments of different parvovirus. Applicants exemplify the effectiveness of the strategy using P1 ligand insertion into VP1 and VP2. Appendix A describes techniques for the identification of assembled viral capsids. APPENDIXES B-D teach examples of mutated structural proteins and their resultant properties (discussed more below).

Applicant's arguments filed 2/19/04 have been fully considered but they are not persuasive. Claims 1-20 and 28 and not just claim 1 are directed towards a mutated structural protein that is capable of particle formation with increased infectivity of viruses containing the mutated structural protein. The specification and the prior art provide methods to produce mutated structural proteins. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for generating it. The protein itself is required in such detail that a person of ordinary skill in the art can recognize what is claimed. Applicants have not demonstrated that they are in possession of the recited genus of mutated structural proteins that can form particles and have increased infectivity. A single disclosed construct, I-587, demonstrates the recited properties. The prior art does not add to this disclosure. Appendix B describes a mutant in which a targeting peptide is inserted into amino acid 587 of the capsid protein with and without an accompanying deletion of 9 base pairs of capsid sequence. Increased infectivity of the mutant is not disclosed. Appendix C and D describe the generation of particles that have mutated structural proteins. Some of the resultant particles have impaired transduction (see page 970, Grifman) and some have altered tropism, whether or not their infectivity is increased is unknown. Therefore, it is unclear whether applicants possess the structural proteins recited in claims 1-20 and 28.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10 and 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Mamounas et al WO 97/38723 publication date October 23, 1997 (provided by applicant), see entire document. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and restated here. The rejection has been extended to newly added claim 28.**

Mamounas et al teach the insertion of targeting molecules into the structural proteins VP-1, VP-2 or VP-3 such that particles result that bind to selected cell types (see e.g. page 4, line 21-31). In conjunction with altered targeting by insertion of a targeting peptide or protein, binding at the wild-type receptor 150 kD heparan sulphate proteoglycan receptor (see e.g. page 3, line 9-15). Envisioned targeting molecules include targeting peptides or proteins such as C4 peptide or monoclonal antibody single chain fragments (see e.g. page 17, line 30 through page 19, line 10). For example, VP-1, VP-2 and VP-3 were incorporated with C4 at their N-terminus (see e.g. page 43, line 28-30) or were mutated to incorporate a single-chain fragment variable region of a monoclonal antibody against the CD34 molecule (sFv) at their N-terminus (see e.g. page 67, line 24-26). Following this mutation, rAAV were produced (see e.g. page 69, line 11-14). The resultant rAAV with sFV fused to VP-2 then was determined to have altered target specificity through interactions with CD34 molecules on KG-3 cells and the rAAV was also shown to have increased infectivity to these cells (page 69, line 15-26 and table 3).

Response to Arguments-35 USC § 102

Applicants traverse the rejection of claims under 35 U.S.C 102(a) as anticipated by Mamounas et al. Applicants argue that the instantly recited claims require the protein be capable of AAV particle formation and Mamounas et al do not teach this element. Applicants argue that none of the recited passages disclose successful production of mutated AAV structural proteins capable of supporting viral particle formation. As a matter of fact, it is said that the construct indicated at page 68, line 13-14 "failed to produce any intact viral particles".

Applicants' arguments filed 2/19/04 have been fully considered but they are not persuasive. The invention of Mamounas et al is a viral particle which has a targeting ligand (see page 3, line 1-8). It is taught that the wild-type viral cell binding site **on the particle** is deleted by deleting nucleic acid sequence which encode the site on a virus corresponding to the vector which interacts with the viral cell binding site and this site is replaced with a targeting ligand (see page 3, line 9-12) Mamounas defines a particle on page 15 as a virally derived vector material which package or is associated with a nucleic acid. In the case of AAV, the particle is a capsid (see page 15, line 4-11) that protects nucleic acid from degradation (page 15, line 16). Specifically on page 26, Mamounas teach that the natural specificity of the AAV capsid was destroyed by mutations to either VP1 or VP3, while the ability of the viral capsid to protect the encapsidation nucleic acid form DNAse I digestion was retained (line 21-24). Mamounas further teaches the production of several AAV mutants and these mutants were transfected into adenovirus infected HeLa cells to produce packaged vector. Intact particle formation was generated by the structural mutant was demonstrated (see page 62, line 24-32). Infectivity of the particles was assessed on page 64. On page 68, line 11-13 Mamounas teaches that **initial**

attempts to make one of their AAV mutant particles failed. However, upon modification of their transfection system, particles with altered structural proteins were generated (see page 68, line 11 to page 69, line 5).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

May 12, 2004

GERRY LEFFERS
PRIMARY EXAMINER